HIMA

HEALTH INDUSTRY MANUFACTURERS ASSOCIATION

July 23, 1998

Dockets Management Branch
Mail Code HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

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Re: Docket No. 98N-0222: Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices - Proposed Rule

Dear Madam or Sir:

These comments are submitted by the Health Industry Manufacturers Association (HIMA) in response to the Food and Drug Administration's (FDA's) proposed rule to implement the provisions of Section401 of the Food and Drug Modernization Act of 1997 (FDAMA) (codified in Sections 551-557 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. §§360aaa through 360aaa-6)) concerning dissemination of off-label information [63 Fed. Reg. 31143 (June 8, 1998)]. HIMA is a Washington, D. C.-based trade association and the largest medical technology association in the world. HIMA represents more than 800 manufacturers of medical devices, diagnostic products, and medical information systems. HIMA's members manufacture nearly 90 percent of the $58 billion of health care technology products purchased annually in the United States, and more than 50 percent of the $137 billion purchased annually around the world.

HIMA supports the goal of these FDAMA provisions to permit educational information on important off-label uses of pharmaceutical, biologic and medical device products to reach health care professionals to benefit patient care. HIMA has the following specific comments on the proposed rule.

Prouosed21 C.F.R. 699.1(b) - Scope

In Section 557(a) of the Federal Food, Drug, and Cosmetic Act it states that nothing in the off-label information dissemination provision "shall be construed as prohibiting a manufacturer from disseminating information in response to an unsolicited request from a health care practitioner." This means that manufacturers are now specifically authorized by statute to provide off-label information to health care professionals in response to their unsolicited requests. This had been a long-standing policy of the FDA, which FDAMA codified.

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Something is missing in FDA's translation of this FDAMA provision to proposed 21 C.F.R. §99. 1(b). The proposed regulation states: "This part [on off-label information dissemination] does not apply to a manufacturer's dissemination of information that responds to a health care practitioner's unsolicited request." Nowhere does the proposed regulation appear to recognize the specific legal authorization for manufacturers to provide off-label information to health care practitioners in response to their unsolicited requests.

HIMA requests that FDA include a statement in the final rule, either in this section or in another appropriate section, to state that manufacturers may disseminate off-label information about human drugs, biologics and devices to respond to a health care practitioner's unsolicited request and that this type of dissemination is not subject to the terms and conditions of this rule.

Proposed 21 C.F.R.§99.3(j) - Definitions

HIMA supports FDA's definition of "supplemental application" in proposed 21 C.F.R. $99.3(j) to include new 5 10(k)s for devices that are the subject of a cleared 510(k) submission. Clearly, the intention of Congress in FDAMA to permit off-label information to be disseminated to health care professionals is intended to apply to all human drug, biologic and device products, irrespective of the type of application that a manufacturer submits to FDA to have such a new use reflected on the product's labeling. Including new 5 10(k)s in the definition of "supplemental application" is an important step in recognizing the intent of Congress and providing full implementation for this provision of FDAMA.

In this spirit, HIMA disagrees with FDA's statement in the preamble of the proposed rule (63 Fed. Reg. at311 45, col. 3) that a new use fora510(k) product that would require a PMA submission is not included in the definition of "supplemental application." It is just as important for health care professionals to have access to this type of off-label information as to the off-label information for uses that require a new 510(k) submission. The form of the submission to FDA is of no consequence to the scientific soundness of the information to be disseminated. The rule should not make an artificial distinction between new 5 10(k)s and new PMAs.

The preamble of the proposed rule points out that some of the new uses to be submitted in supplements for drugs and devices that are within the purview of these off-label information dissemination provisions include: "[a] completely different indication; modification of an existing indication to include a new dose, a new dosing schedule, a new route of administration, a different duration of usage, a new age group (e.g. unique safety or effectiveness in the elderly), another patient subgroup not explicitly identified in the current labeling, a different stage of the disease, a different intended outcome (e.g. long-term survival benefit, improved quality of life, disease amelioration), effectiveness for a sign or symptom of the disease not in the current labeling; and comparative claims to other agents for treatment of the same condition." (63 Fed.

Reg. at 31145, cols. 2-3). There is no reason to eliminate from the off-label dissemination provisions these same new uses simply because in some cases a PMA (rather than a new 5 10(k)) would be required to place such a new use on a device's label.'

HIMA requests that FDA specifically include within the definition of "supplemental application" a PMA submission for a new use of a product cleared through the 510(k) process.

Proposed 21 C.F.R. § 99.101 (b)(1) - Information that may be disseminated

In this section, FDA articulates a number of prescriptive criteria for determining whether a clinical investigation is "scientifically sound" for purposes of dissemination of off-label information. These are: a description of the study design and conduct, data presentation and analysis, summary of results, and conclusions pertaining to the new use.

The preamble discussion of "scientifically sound" contains even more narrowly focused, restrictive criteria. (63 Fed. Reg. at 31146, col. 3 and 31147, col. 1). These mandate the published clinical investigation to: be prospectively planned, enroll an appropriately defined patient population, account for all patients enrolled, including all patients who discontinued therapy prematurely, use clinically meaningful endpoints, use a well described treatment regimen, use an appropriate control group, collect and report adequate information on adverse reactions, and be analyzed in a scientifically appropriate manner.

This FDA approach is much too restrictive and will result in few, if any, scientific or medical journal articles being disseminated. HIMA believes that if an investigation is peer reviewed and published in a scientific or medical journal (as defined in Section 556 of the FFDCA), the FDA regulation should establish a presumption that it is "scientifically sound." The final rule should explicitly state this presumption.

Indeed, many valuable published investigations may not contain information relevant to the criteria listed in the proposed regulation and preamble. This does not mean that the investigation is not scientifically sound. The publication of the investigation is intended to be distributed to health care professionals. They will recognize the limitations in the information and make their

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[1] HIMA disagrees with the agency's characterization of a different intended outcome (e.g. long-term survival benefit, improved quality of life, disease amelioration) as an off-label use. Claims related to outcome, such as performance claims, do not change the intended use or indications for use of the product or alter the safety and effectiveness of the product. Providing this type of additional information about an existing approved use should not require FDA approval. In fact, such claims do not require PMA supplements pursuant to 21 C.F.R. $814.39 and therefore are not to be considered off-label uses.

own judgments. FDAMA does not contain these restrictive criteria, and therefore the agency should not consider them to be necessary findings for a determination of "scientifically sound." If the agency thinks these criteria should be addressed, the final rule can require that any limitations in these details be disclosed by manufacturers to the health care professionals as part of the off-label information dissemination.

Pro~osed21 C.F.R. 699.103(a)(2) - Mandatory statements and information

This proposed section refers to the official labeling of a drug or device, which is required to be distributed by a manufacturer with the off-label use information. The discussion of official labeling in the preamble of the proposed rule (63 Fed. Reg. at 31147, col. 3) notes that the official labeling is the package insert for drugs but because devices "do not always include a package insert in the same form and manner as drugs," device manufacturers are to provide: the name of the device, including its trade or proprietary name, the manufacturer's name, address, and telephone number; a statement of intended use, including a general description of the diseases or conditions that the device is intended to diagnose, treat, cure, or mitigate, a description of the patient population for which the device is intended, a description of indications that have been approved or cleared by FDA, a description of any limitations or conditions that have been placed on the sale, distribution, or use of the device, and all warnings, contraindications, side effects, and precautions associated with the use of the device.

HIMA requests that a device's "official labeling" be defined as either: (a) the package insert for the device or (b) the accompanying documents that a manufacturer distributes with its legally marketed device to comply with the requirements of21 C.F.R. Part 801 or21 C.F.R. $809.10 for in vitro diagnostic products or (c) a new labeling vehicle (in effect, a package insert) created by a manufacturer that contains the listed items from the preamble's discussion. In this way, device manufacturers can have the flexibility to disseminate the labeling most applicable to a particular device along with the off-label information.

Proposed 21 C.F.R. 699.201(a)(2) - Manufacturer's submission to the agency

Manufacturers are required to submit to FDA a copy of the off-label information to be disseminated and any other clinical trial information the manufacturer has relating to the safety or effectiveness of the new use. With respect to the clinical trial information, HIMA suggests that the rule should permit manufacturers to reference existing files submitted to FDA (such as INDs, NDAs and/or NDA supplements, IDEs, 5 10(k)s, PMAs and/or PMA supplements) that may contain this information, rather than requiring manufacturers to resubmit it. The rule should also make clear that FDA will maintain the confidentiality of all such information, as this type of clinical trial information has traditionally been treated as confidential pursuant to FDA regulation.

Proposed 21 C.F.R. $$99.201 (a)(4)(I)(B) and (a) - Manufacturer's submission to the agency

Each of these sections contains specific language for a certification to besigned byan authorized official of a manufacturer, regarding completion of clinical studies and submission of a supplemental application to FDA. HIMA believes the language in these certifications should include the introductory phrase "to the best of my knowledge." Such a modification reduces the risk that a certifying official could be penalized for situations in which inadvertent mistakes occur in the processing of information that are not within the knowledge base available to the certifier. Incorporating this additional language will reduce the regulatory burden to certifying officials.

Proposed 21 C.F.R. $99.205- Application for exemption from the requirement to file a supplemental application

Proposed 21 C.F.R. $99.205 (b)(1)(ii) outlines criteria for determining whether filing a supplemental application for a new use is "economically prohibitive." The formula proposed is whether the cost of studies for the new use exceeds the total revenues from the device (including revenues from approved uses) minus costs and expenses attributable to the device. In HIMA's view, this is not the correct formula. Instead, the formula should be whether the cost of studies of the new use exceeds the projected revenue of the new use of the device. This is the more realistic way in which a manufacturer would decide whether it makes sense financially to pursue the development and regulatory approval of a new use. Section 554(d)(2)(A) of the FFDCA, in describing the concept of economically prohibitive, is focused on the new use. The FDA regulation needs to maintain this focus. The currently proposed formula would virtually destroy this exemption, since it is an impossibly severe test. Even though Congress intended exemptions to be rare, it did intend for them to be achievable.

Proposed 21 C.F.R. $99.205 (b)(1)(ii)(A) requires that, in determining whether a supplemental application is economically prohibitive, the manufacturer must assume that the potential market for the device is equal to the prevalence of the disease or condition treated. This is not a reasonable assumption and it has no basis in FDAMA. There may be many reasons why a device is not useful in a subpopulation and thus the prevalence of the disease is not an accurate measure of the potential market. This requirement should be deleted from the rule.

Instead of any rigid, formulaic approach, a manufacturer should be given the flexibility to present whatever information it determines is relevant to the "economically prohibitive" factor. Manufacturers will vary greatly in their economic situations. Each situation should be presented and evaluated on a case-by-case basis. A manufacturer should be able to state its own

assumptions in determining the potential market for the product. For example, an economic analysis may include a specified time period over which the costs and revenues are considered. FDA can then evaluate the reasonableness of these assumptions.

The preamble of the proposed rule invites comment on whether requests for exemptions from filing supplemental applications on grounds of the cost being economically prohibitive are to be accompanied by a report of an independent accounting firm verifying the cost estimates (63 Fed. ~at311 49, co1. 2). FDAMA does not contain any such requirement. In HIMA's view, such a requirement would be expensive and unnecessary. The final rule should not contain any such requirement.

The preamble of the proposed rule also invites comment on whether, to demonstrate "economically prohibitive," the manufacturer must show that "the cost[s] of conducting the studies needed for the supplement substantially exceed revenues and [are] unusually great compared to the typical costs of developing products for similar uses." (63 Fed. Reg. at 31149, co1. 3). FDAMA does not contain any such requirement. HIMA believes that it is unduly restrictive and should not appear in the final rule.

Proposed 21 C.F.R. $99.205(b)(2) defines the circumstances in which an exemption from the supplemental application requirement will be granted on the grounds that the necessary studies are unethical. FDA states that a study would not be considered unethical unless withholding of the device in the course of a controlled clinical trial would pose an unreasonable risk of harm to human subjects, which would generally arise only in situations in which the intended use of the device appears to affect mortality or irreversible morbidity. FDAMA does not contain any such restrictions. HIMA believes this criterion for determining whether a study is unethical is unreasonably restrictive. It should be deleted.

To determine whether a necessary study is unethical, FDAMA requires FDA to consider whether the new use has become the standard of medical care. In HIMA's view, this means that FDAMA intends there to be a presumption that conducting a study for a new use that has become the standard of care is unethical. Surely, once a treatment becomes the recognized standard of medical care, physicians will not subject patients to a controlled study involving that new use, particularly if the study includes a placebo group. The proposed rule takes a different posture by describing evidence that a new use has become the standard of care as merely information to "add weight" to the argument that a study is unethical, rather than in and of itself sufficient to support such a finding. HIMA requests that FDA rework this section in the final rule, to give deference to a finding that a new use has become the standard of care.

Pro~osed21 C.F.R. ~99.401 - Corrective actions and cessation of dissemination of information

In proposed21 C.F.R. $99.401(d), it states that an order to cease dissemination of information shall be effective upon the date of issuance by FDA, unless otherwise stated in such order. On the date of the issuance of an order by FDA, a manufacturer may have no knowledge that such an order has issued. It would be more efficient to provide that an order to cease dissemination of information is effective upon the date of the order's receipt by the manufacturer. HIMA requests that the final rule state that an order to cease dissemination of information is effective on the date of its receipt by the manufacturer.

In addition, it is unlikely that a manufacturer can stop the dissemination of information everywhere in the United States on the same date that it receives an order to cease dissemination. It would be more reasonable for a manufacturer to have a period of time in which to comply with the order - such as the 60 day time frame provided in proposed21 C.F.R.§99.403(c) for termination of an exemption from the requirement to file a supplemental application accompanied by an order to cease dissemination of information. HIMA requests that the final rule provide a 60-day time period for a manufacturer to comply with an order to cease dissemination of off-label information.

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HIMA appreciates the opportunity to submit these comments.

Respectfully submitted,

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and Associate General Counsel